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In re Patent Application of:
Anna Helgadottir

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For: SUSCEPTIBILITY GENE FOR MYOCARDIAL INFARCTION AND STROKE

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Examiner: J.A. Goldberg

DECLARATION OF ANDREI MANOLESCU, PH.D., UNDER 37 C.F.R. § 1.132

I, Andrei Manolescu, hereby declare as follows that:

1. I am a scientist and statistician who has worked at deCODE genetics, ehf. ("deCODE') since 1999 as a statistician and research scientist. My *curriculum vitae* is attached hereto.

2. I am familiar with the above-identified U.S. patent application and deCODE's research project involving the association between FLAP haploytpes and increased risk for myocardial infarction. I have been involved as part of the research team at deCODE that studies this association and have personally been involved in the statistical analysis of data from which the correlation between FLAP haplotypes and MI has been observed and confirmed. I am providing this declaration to make available to the Examiner additional data and analysis of this phenomenon. I have personal knowledge of the information in this declaration, and my use the pronoun "we" refers to the deCODE team involved in this research project, of which I am a part.

The discovery of HapA and the replication studies in deCODE

3. In 2004 deCODE discovered and published the association of a haplotype variant of the FLAP gene (5-lipoxygenase activating protein, also known as ALOX5AP) with Myocardial Infarction (MI) and stroke in an Icelandic cohort of 779 MI patients, 702 Stroke patients, and 624 population controls. We called it HapA and it was defined by four single nucleotide polymorphisms

(SNPs) in linkage-disequilibrium situated within the gene in an interval of 33 kilobases: G SG13S25, T SG13S114, G SG13S89, A SG13S32. We selected this haplotype after a large number of statistical tests identifying it as significantly associated with MI. The odds ratio (OR) was 1.8, and the association remained significant after correcting for multiple comparisons with P=0.005 (Helgadottir et al, 2004).

4. After the discovery of HapA deCODE published a replication of the association with stroke in a Scottish cohort (Helgadottir et al., 2005).

5. The deCODE research team has collected more data to evaluate the association of FLAP HapA with increased risk of MI. We have genotyped a second Icelandic cohort of 1441 cases and 9811 control individuals who were not used in the discovery phase (here called Iceland 2), and six other foreign cohorts. HapA showed a significant association in Iceland 2, but weaker than in the original cohort Iceland 1, with OR=1.15. (See Table 1 below.). This lower OR suggests that the magnitude of the OR initially detected may have been inflated by the selection process. In the groups of patients and controls of Iceland 2 the allelic frequencies were by almost 2% lower and higher respectively, than in Iceland 1. However, the observed association in the Iceland 2 study was statistically significant.

6. We further studied HapA in six non-Icelandic cohorts: four from the United States, one from the United Kingdom (the same cohort as was used in the initial publication Helgadottir et al 2004) and one from Italy (Verona). The association was in the opposite direction (OR<1) in the U.S. group from Philadelphia. All of the other cohorts had OR that were greater than 1 and comparable in magnitude to that in Iceland 2, but only one nominally significant. Results for the Italian cohort have been already published by Girelli et al. (2007): they found no statistically significant association of HapA to MI. We received their samples including a set of additional population controls and genotyped them at deCODE. The results for those are shown in Table 1.

7. We combined the genotype data of the non-Icelandic cohorts using the Mantel-Haenszel model, which estimates a common OR assuming different haplotype frequencies for each group (Mantel and Haenszel, 1959; Woodward, 2005). The result was again significant and very similar to the one obtained in Iceland 2 (Table 1). When the data from all of our replication groups (six non-Icelandic plus Iceland 2, but not original Iceland 1) are pooled, the estimated OR is 1.11 with

P=0.00054. These results show that the variant HapA is significantly associated with MI, but the effect is systematically weaker than in our initial publication, and therefore an increased statistical power is needed to replicate it. The OR in the replication groups is free of any selection bias that could have been present in the Iceland 1 cohort.

Replication studies of HapA outside deCODE

8. To my knowledge, publications derived from three additional studies, for which we have no access to genotypes, have reported results on HapA association with MI. Zee et al. conducted a study of two groups, 341 MI case-control pairs and 259 stroke case-control pairs, all white males from USA matched in pairs by age and smoking. They found HapA in excess in both type of patients relatively to the controls, but not significantly, OR=1.18 P=0.46 for MI and OR=1.11 P=0.71 for stroke. Their analysis was done in a different way than ours, by logistic regression with adjustments for several factors. We thought these adjustments were not necessary, but rather induced some noise. We also thought the case-control pairing was not necessary, but rather reduced the statistical power. Therefore we joined their controls into a single control set and using only their estimated haplotype frequencies we recalculated for the MI patients OR=1.23, and P=0.058 (using a simple one-sided Chi-squared test with one degree of freedom).

9. In a second publication, Koch *et al.* studied a large set of MI cases and controls from Germany, where again HapA was found in a slight, but not statistically significant, excess in patients.

10. A third paper, by Morgan *et al.*, analyzed data for patients with acute coronary syndrome, i.e. MI or unstable angina, a phenotype slightly different than ours. Morgan *et al.* reported that the HapA frequency was a little lower in the patients than in the controls. In Table 1 we show our results corresponding to the Zee study, but the original results by Koch and Morgan, with one-sided P-values.

Meta-analysis of combined results from deCODE and outside

11. As a statistician with experience studying population genetics, it is my opinion that the results of the other studies are not in contradiction to deCODE's data indicating a statistically significant association between the presence of FLAP HapA and increased risk of MI. In this section of my

declaration I explain my analysis of all of this data.

12. We performed a meta-analysis of all available results, including data from cohorts genotyped at DeCODE and the three external studies. Since we do not have the genotype data behind the external studies, we cannot use the Mantel-Haenszel method in the way we used it for joining the cohorts for which we have genotypes. Instead we can use the more empirical solution of adding the Z-scores of each study *s*, Z_s (i.e. the standard normal value corresponding to the one-sided P-value) with positive or negative signs if OR>1 or OR<1 respectively, and with weights w_s given by the inverse of the standard errors of the OR estimates:

$$Z = \left(\sum_s w_s Z_s\right) \Big/ \sqrt{\sum_s w_s^2} \,,$$

where $w_s = Z_s / \log(OR_s)$. We assume the OR's have log-normal distributions. The combined OR is then given by the formula:

$$\log(OR) = \left(\sum_s w_s^2 \log(OR_s)\right) \Big/ \left(\sum_s w_s^2\right)$$

Again, to avoid the initial selection bias the group Iceland 1 was not included in the meta-analysis.

13. We considered the seven internal replication groups as a single complex cohort represented by the joint P-value and OR already calculated (Table 1). The joint P-value of the four studies, one from deCODE and three external, was 0.00034 and the joint OR=1.11 (Table 1). By adding the external results, with one in the negative direction, the association of HapA to MI became even more significant, the overall P-value was reduced, and the joint OR did not change. Using also the original OR and P-value of Zee et al. for MI, instead of the values recalculated by us, we obtained similar results.

Table 1. Meta-analysis of results using data from deCODE and published results for HapA

Cohort (cases/controls)	*P*	OR (95% CI)	MI	Controls
Iceland 1 : Nat.Genet.36, 233 (2004)	0.0050	1.80	0.158	0.095
Iceland 2 (1441/9811)	0.013	1.15	0.140	0.124
European Americans				
Philadelphia (725/516)	0.746	0.93	0.159	0.170
Cleveland (653/618)	0.027	1.27	0.162	0.133

Atlanta (762/1302)	0.013	1.24	0.174	0.146
Durham, NC (1314/739)	0.183	1.09	0.146	0.135
United Kingdom (750/726)	0.211	1.09	0.169	0.157
Italy (657/1079)	0.271	1.06	0.181	0.172
All MI Caucasian foreigners (4861/4980)	0.008	1.11 (1.02,1.21)		
All Caucasians replication Iceland 2 + US + UK + Italy (6302/14791)	0.00054	1.12 (1.05,1.20)		
Other studies				
Zee et al. (341/600)	0.058	1.23	0.172	0.145
Koch et al. (3657/1211)	0.080	1.10	0.160	0.148
Morgan et al. (811/ 650)	0.840	0.90	0.152	0.165
All replication studies combined	0.00034	1.11 (1.05,1.18)		

Discussion

14. Combining results from several studies is important for estimating the overall effects. It is a way of balancing out the deficiencies in each individual study, like different or insufficient matching of cases and controls. But most importantly combining the results of studies is a way of gaining statistical power by increasing the sample size. Statistical power is essential, especially for a genetic variant whose observed effect is weak, in order to demonstrate a true underlying effect. That is why the meta-analysis is now the state of the art in the genome-wide association (GWA) studies with hundreds of thousands of SNPs.

15. In order to prove the genome-wide significance of a SNP with OR about 1.2 or less, which is usually observed, one needs thousands of cases and controls, which can only be obtained by combining several cohorts together. For example, Easton et al. (2007) combined more than 20 cohorts in order to demonstrate the association of five different SNP's with breast cancer. The overall ORs for these SNPs varied between 1.26 and 1.06, comparable to our result for HapA. The individual ORs for each cohort were spread over a broad interval and some ORs were even smaller than one (Easton et al, Table 2 and Figure 2). In terms of P-values, this means that each cohort had a small contribution, possibly not even nominally significant, but the combined result was statistically significant.

16. Another example is provided by the recent study on prostate cancer, by Gudmundsson et al. (2007). Two variants are shown to be associated with the disease by joining four cohorts from Iceland, Holland, Spain, and USA, with OR=1.2. For both variants, the cohort from Spain did not show significant association (Gudmundsson et al., Table 2 and 3), but the combined P-value was significant. Indeed, a significant P-value in a genome-wide association study has to be much lower than our combined P-value of 0.00034 for HapA, because of the large number of genetic variants tested. Instead we tested only one variant, and our P-value is far below the conventional threshold of 0.05. It would correspond to a P-value of the order of 10^{-9} in a GWA study.

Conclusions

17. We conclude, based on the meta-analysis of all available data, that the FLAP HapA variant is truly associated to an elevated risk for MI. It is my opinion as a statistician that population geneticists and other statisticians would share my opinion that the meta-analysis approach is valid and appropriate and that the association between FLAP HapA and MI is real, based on the available data The modest OR may indicate that HapA is not functionally causative of MI, but rather a valid surrogate of a yet unknown variant with higher penetrance. This does not change the relevance of the HapA as a diagnostic tool for determining which individuals are at increased risk of developing MI due to the presence of HapA – the effect being about 11% for each copy of HapA present in the genome of an individual.

18. An increase in risk of 11% is by no means insignificant, and can be compared to biomarkers and physiological measures which are generally believed to affect risk of developing cardiovascular disease in a quantitative manner (*e.g.*, blood pressure, cholesterol levels) (Wilson et al. 1998). Also, similar effects to those we observe for HapA have been found for variants recently discovered in published GWA studies and are typical for common polymorphisms in common diseases. My opinion as a statistician (which other statisticians would share) is that one judge's whether an observed increase in risk is a "real" phenomenon based on the overall P-value, and not by the magnitude of the OR. P-value indicates statistical significance, whereas OR indicates the magnitude of the increased risk.

19. The results of the meta-analysis confirm that the association between FLAP HapA and increased risk of MI is indeed significant when combining all available studies. In view of this data,

the HapA status of individuals can be used to determine their individual risk of developing MI – quantitatively determined to be about 11% for each copy of the variant carried by the individual. Moreover, ou data identify FLAP as a therapeutically attractive target for MI prophylactic agents.

Statistical methods

20. In each replication test we tested the hypothesis that HapA is in excess in patients, i.e. OR>1, and the P-values displayed in Table 1 are therefore 1-sided. The OR's are calculated assuming the multiplicative model (Falk 1987, Terwilliger 1992). The results for Iceland are corrected for relatedness by simulating genotypes through the Icelandic genealogy (Grant et al., 2006). The deCODE data was analyzed with the software NEMO (Gretarsdottir et al. 2003). NEMO handles uncertainty of phase and missing genotypes through a likelihood procedure using the expectation-maximization algorithm to estimate haplotype frequencies (Lange 2002). Relative to Table 1 included in inventor Helgadottir's declaration (January 2007) for this patent application, in the present version of Table 1 we updated the lists of patients and controls for each cohort and we included the Italian cohort from Verona.

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22. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Dated: Oct. 16 2007 A Manolescu

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Education
1978-1983: University of Bucharest, Faculty of Physics.
1989-1992: doctorate at the Institute of Atomic Physics, Bucharest;
Thesis: "Contributions to the study of the response and correlation functions in quantum many-body systems"
Positions
1983-1985: physicist at Machine-Tools Factory, Bucharest, nondestructive defectoscopy.
1985-1999: research position at the National Institute of Materials Physics, Principal Researcher 1 since 1995 (the highest rank).
1995-2002: Associate Member of the International Centre for Theoretical Physics, Trieste, Italy.
1999-2007: Statistician, Research Scientist at Decode Genetics, Reykjavik, Iceland.

Academic title: Doctor in Physics since 1992.
Expertise in genetics
Statistical analysis of genetic data for linkage and association of genes with complex diseases. Cardiovascular diseases: myocardial infarction, stroke, atherosclerosis, hypertension. Cancer: prostate cancer, breast cancer. Linkage disequilibrium and haplotype analysis. Quantitative trait analysis by linear regression methods. Population stratification.

Expertise in physics
Two-dimensional systems in magnetic fields, screening, exchange, and other many-body Coulomb effects, edge states, transport and electromagnetic absorption in modulated systems, electronic states in periodic electric and magnetic fields, spin splitting, magnetization.
Teaching experience at University of Bucharest (1986-1987) and at University of Iceland (1998-2002).

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